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REVIEW ARTICLE

Intravascular ultrasound-guided drug-eluting stent implantation

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Abstract Intravascular ultrasound (IVUS) is a reliable imaging tool to guide percutaneous coronary intervention. There has been increasing evidence supporting the clinical utility of IVUS-guided drug-eluting stent (DES) implantation, including randomized trials, observational studies, and meta-analyses of both. IVUS provides cross-sectional views of the coronary artery wall, and allows us to assess stenosis severity, identify plaque morphology, optimize stent implantation, and understand mechanism of stent failure. IVUS guidance can increase DES efficacy and decrease clinical events. In this review article, we summarize available evidence on IVUS-guided DES implantation.

Keywords Intravascular ultrasound · Percutaneous coronary intervention · Drug-eluting stent · Stent thrombosis · Restenosis

Introduction

Intravascular ultrasound (IVUS) has been used clinically for more than 20 years and established as a reliable imaging tool to guide percutaneous coronary intervention (PCI). In Japan, IVUS is utilized in over 80% of PCI procedures [1]. IVUS provides cross-sectional views of the coronary artery wall, and allows us to optimize stent implantation and understand mechanism of stent failure (thrombosis and restenosis) that can be missed using coronary angiography. In this review article, we summarize available evidence on IVUS-guided drug-eluting stent (DES) implantation.

IVUS- versus angiography-guided DES implantation

IVUS-guided DES implantation has been reported to influence treatment strategy and provide better clinical outcomes compared with angiography-guided DES implantation [2–7]. A recent meta-analysis, involving 7 randomized trials and 18 observational studies with 31,283 patients, found that IVUS guidance reduced major adverse cardiac events, death, myocardial infarction, stent thrombosis, and target lesion and vessel revascularization [2]. In ADAPT-DES (Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents) [3], the largest observational study of IVUS use to date, IVUS guidance was associated with reduced 1-year rates of stent thrombosis, myocardial infarction, and major adverse cardiac events, as well as target lesion and vessel revascularization. The benefits of IVUS guidance were evident in patients with acute coronary syndromes and complex lesions. Based on IVUS findings, the operators changed the PCI strategy in 74% of patients and used a larger stent/balloon, a longer stent, higher inflation pressures, additional post-dilatation, and additional stent placement. In meta-analyses of 7 randomized trials, including 3192 patients, a favorable result for IVUS-guided DES implantation was found for major adverse cardiac events, target lesion revascularization, and target vessel revascularization [2, 4], although the benefits were influenced by the IVUS-XPL (Impact of Intravascular Ultrasound Guidance on Outcomes of Xience Prime Stents in Long Lesions) study, having almost half of the patients [5]. A pooled analysis from 4 Spanish registries showed

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that IVUS-guided DES implantation in patients with left main coronary artery (LMCA) disease was associated with better clinical outcomes, especially in those with distal LMCA disease [6].

Pre-intervention lesion assessment

Stenosis severity of non-LMCA disease

To date, most available data regarding the relationship between IVUS minimum lumen area (MLA) and functionally significant stenoses in non-LMCA lesions have been from retrospective data analyses. IVUS MLA cutoff values range from 2.1 to 4.0 mm^2 and best correlate with physiology [8–18]. The traditional MLA cutoff value has been 4.0 mm^2. However, recent studies have reported smaller cutoffs or different cutoffs for different diameters and vessel locations [11, 12]. Overall, the common cutoff value is approximately 3.0 mm^2 [19]. Most IVUS studies showed a relatively high negative predictive value but a low positive predictive value. It indicates that IVUS MLA cutoffs are not suitable for justifying the need for revascularization, but suitable for deferring revascularization. Waksman et al. reported in a prospective registry that the optimal MLA cutoff value correlated with a fractional flow reserve of <0.80 increased with reference vessel diameter. The MLA cutoff for the total cohort was 3.07 mm^2 with a positive predictive value of 40% and negative predictive value of 83%. The MLA <2.4 mm^2 was the best cutoff for vessel diameters <3.0 mm, MLA <2.7 mm^2 for vessel diameters of 3.0–3.5 mm, and MLA <3.7 mm^2 for vessel diameters >3.5 mm [11]. Another study showed that the MLA cutoff was 3.0 mm^2 for proximal left anterior descending (LAD) artery lesions and 2.75 mm^2 for mid LAD lesions located before the second diagonal branch, although appropriate cutoffs could not be found in other segments [12].

Stenosis severity of LMCA disease

Previous studies have shown that a high percentage of patients with an angiographically normal LMCA have disease when assessed by IVUS [20, 21]. The most frequently recommended MLA value for LMCA stenosis is 6 mm^2. This value was primarily calculated from Murray's law, with an MLA of 4.0 mm^2 that was considered to represent the ischemic threshold of the LAD or LCX, and was supported by several prospective studies [22, 23]. On the other hand, Park et al. reported that an MLA of <4.5 mm^2 was an independent predictor of a fractional flow reserve of <0.80 [24]. This value is consistent with the application of Murray's law to the recently reported MLA values of 3.0 mm^2 for ostial LAD or LCX. Additionally, they found that plaque rupture was an independent predictor of functionally significant LMCA disease. Theoretically, complex or irregular lesions and thrombus can produce greater flow resistance and energy loss of fluid. The limitations of IVUS analysis for LMCA are the potential lack of coaxiality and subsequent lumen distortion [23].

Plaque rupture

Intravascular ultrasound morphology of plaque rupture is characterized as a ruptured plaque containing a cavity that communicated with the lumen with an overlying residual fibrous cap fragment [25] (Fig. 1). In patients with acute coronary syndrome, plaque rupture occurs in 60–65% of cases [19, 25, 26]. However, in the VANQWISH (Veterans Affairs Non-Q-Wave Infarction Strategies in-Hospital) study, angiography could not identify culprit lesions in 37% of patients with acute coronary syndrome [27]. On the other hand, previous IVUS studies showed that IVUS allowed to detect plaque ruptures in one half of ST-segment elevation myocardial infarction culprit lesions [25, 28].

Attenuated plaque

Attenuated plaque is hypoechoic or mixed atheroma with ultrasound attenuation without calcification [29] (Fig. 1). The common pathological feature is the presence of a thin-cap fibroatheroma that is responsible both for the IVUS findings and for periprocedural myocardial infarction during stent implantation [30]. A large-scale registry reported that no-reflow occurred in 2.3% of the patients with acute myocardial infarction during the PCI procedure [31]. Endo et al. reported that the incidence of no-reflow was 15% in patients with plaque rupture, 20% in patients with attenuated plaque (angle ≥180° and length ≥5 mm), and 88% in patients with both [32]. Another study reported that mean attenuation angle ≥90° best-predicted no-reflow [29]. Conversely, the absence of these findings indicates a low probability of a periprocedural myocardial infarction. The short- and long-term outcomes of PCI for acute myocardial infarction have been reported as unfavorable in patients with no-reflow phenomenon [31, 33].

Spontaneous coronary artery dissection

Spontaneous coronary artery dissection is an unusual culprit lesion morphology that can be detected by IVUS in patients with acute coronary syndrome (Fig. 2). The use of IVUS is helpful in patients for whom the

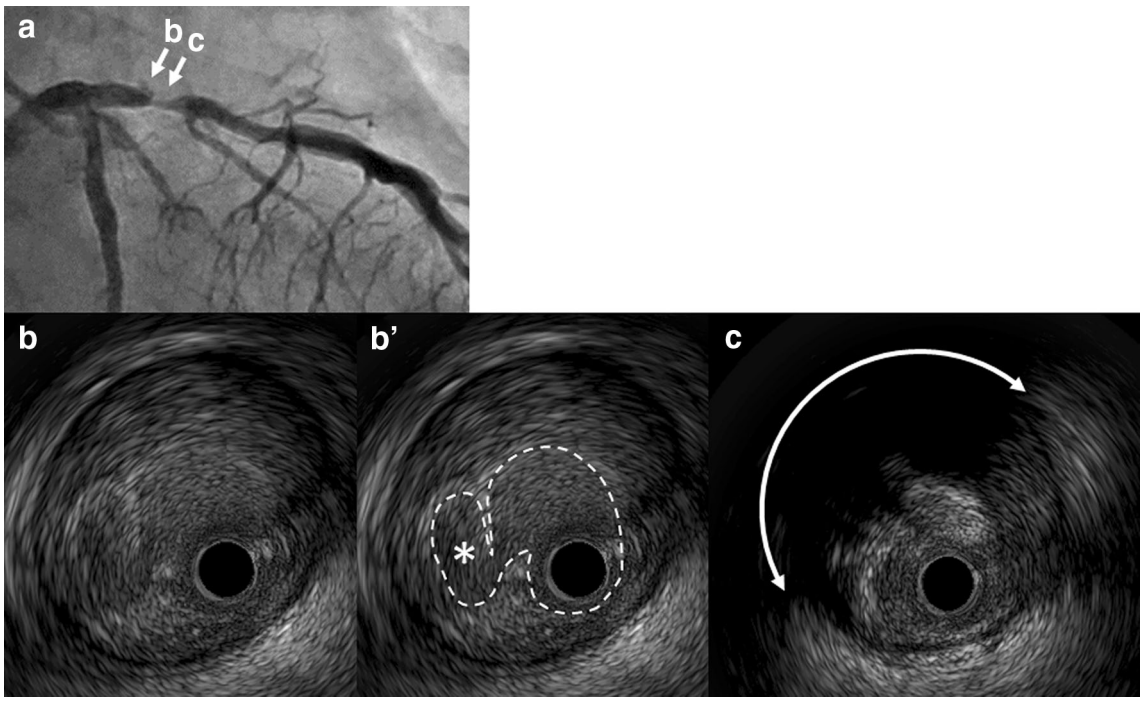

Fig. 1 Plaque rupture and attenuated plaque. A 74-year-old male presented with an acute coronary syndrome. Coronary angiography shows a culprit lesion in the proximal left anterior descending artery (**a**). Intravascular ultrasound reveals a ruptured plaque (**b**, **b**′) with a cavity (*asterisk*) and an attenuated plaque (**c**) that is hypoechoic atheroma with ultrasound attenuation without calcification (*double-headed white arrow*)

diagnosis of spontaneous coronary artery dissection is considered but not secured with angiography. Since several studies have reported the natural spontaneous healing of dissected arteries, conservative management for stable patients may be optimal [34, 35]. However, it should be considered that patients presenting with acute myocardial infarction who have symptoms of ongoing ischemia or hemodynamic compromise undergo revascularization with PCI or coronary artery bypass grafting [34, 36]. IVUS-guided PCI for spontaneous coronary artery dissection is essential to prevent inadequate or excessive stent coverage and to reduce the risk of progression following stenting [37].

Heavily calcified lesions

Heavily calcified lesions are a challenging subset, which may lead to failure of stent delivery or expansion and may increase the likelihood of stent thrombosis and restenosis. Moreover, heavily calcified lesions may damage the polymer/drug coating during vigorous advancement [38, 39] (Figs. 3, 4). Although routine rotational atherectomy did not improve DES efficacy, rotational atherectomy remains an important tool for uncrossable or undilatable lesions and improves procedural success in this setting [40, 41]. A previous study reported that rotational atherectomy was more frequently used in IVUS-guided PCI than angiography-guided PCI, which may have been associated with reduced rates of repeat revascularization and stent thrombosis [7].

Heavily calcified lesions are a risk factor of coronary artery perforation [42, 43], which may be caused by the use of rotational atherectomy, as well as oversized balloons/stents. Eccentrically calcified plaques along with a normal segment (Fig. 5) may be also at risk of coronary artery perforation due to overstretching the normal segment. IVUS guidance could prevent a marked mismatch between balloon/stent diameter and vessel diameter and reduce coronary artery perforation.

Positive and negative remodeling

Intravascular ultrasound is more sensitive than angiography in detecting early coronary atherosclerosis. Development and progression of coronary artery stenosis is a balance between plaque accumulation and positive remodeling [44]. Previous studies have shown that positive remodeling was more common in patients with acute coronary syndrome and that the degree of positive remodeling was greater in acute myocardial infarction

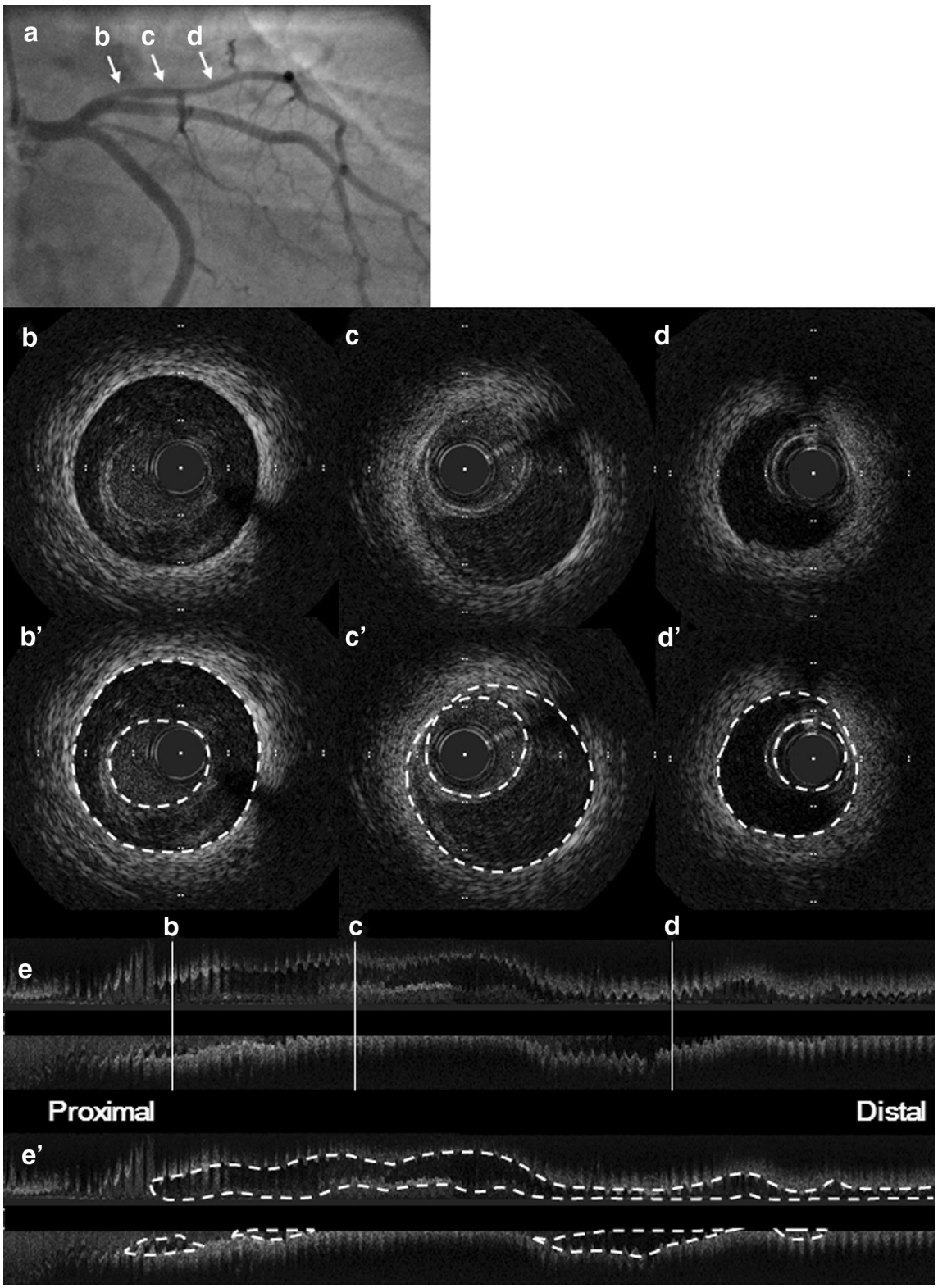

Fig. 2 Spontaneous coronary artery dissection. A young woman presented with an acute coronary syndrome. Coronary angiography shows a diffuse intermediate stenosis in the proximal and middle left anterior descending artery (**a**). Intravascular ultrasound images (**b**–**e**) showed diffuse, massive, circumferential, intramural hematoma without intimal dissection (*dotted lines* in **b**′–**e**′)

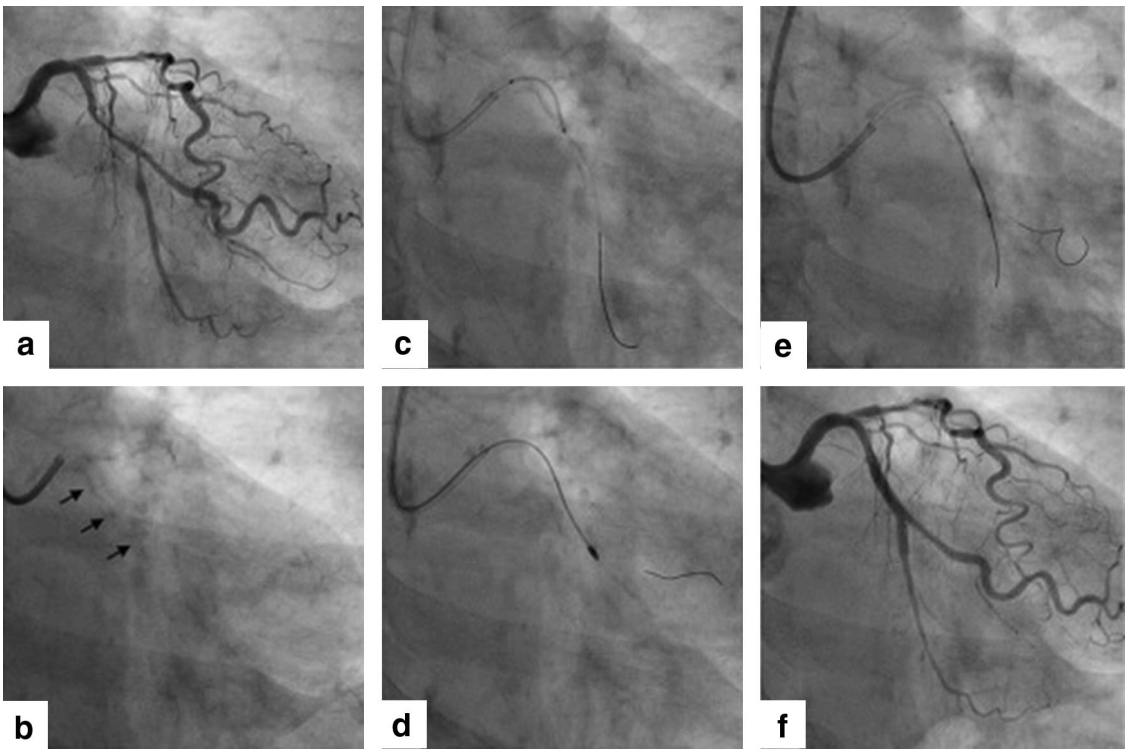

Fig. 3 Everolimus-eluting stent implantation in a calcified coronary artery. Coronary angiography showed an 80% stenosis in the mid left circumflex artery (**a**). Fluoroscopy demonstrated calcification (*arrows*) in the proximal and mid left circumflex artery (**b**). An everolimus-eluting stent was not able to advance to the lesion (**c**). Rotational atherectomy was performed (**d**). Another everolimus-eluting stent advances to the lesion without significant resistance (**e**). The final angiogram showed a good result (**f**). Reprinted from Kuriyama et al. [38]

than in unstable angina. Conversely, negative remodeling was more common in patients with stable angina [45, 46].

Bifurcation lesions

Coronary plaques at bifurcation lesions are localized opposite to the side branch and plaque accumulates opposite the flow divider [47]. Previous studies have reported that angiographic predictors of side branch occlusion were the diameter stenosis at the ostium of side branches and the angle between the main vessel and side branch [48, 49]. Several IVUS studies have reported that IVUS predictors of side branch occlusion were the presence of plaque at the side branch ostium, the main vessel plaque thickness at the junction site, and the side branch diameter ratio (defined as side branch vessel diameter/side branch lumen diameter) [50, 51]. In LMCA bifurcation lesions, IVUS should be performed from both the LAD and LCX to accurately assess the entire disease. An IVUS study reported the plaque distribution at the distal LMCA bifurcation [47]. The most common IVUS pattern involved continuous axial plaque from the distal LMCA into the proximal LAD and LCX arteries (62%). An additional 28% of distal LMCA bifurcations had continuous plaque from the distal LMCA into the LAD with or without focal plaque at the ostial LCX.

Optimization of DES implantation

IVUS predictors of early stent thrombosis and restenosis in the DES era

IVUS studies have revealed that the predictors of DES early thrombosis or restenosis are stent underexpansion and residual edge disease (dissections, stent edge plaque burden, and residual edge stenosis) [52–64]. There is no data linking isolated acute stent malapposition without stent underexpansion to early stent thrombosis or restenosis [19, 65–68], although persistent stent malapposition following acute stent malapposition is associated with late/very late stent thrombosis [69, 70]. These IVUS studies also suggest that the mechanisms underlying early stent thrombosis are mechanical and potentially treatable when identified by IVUS.

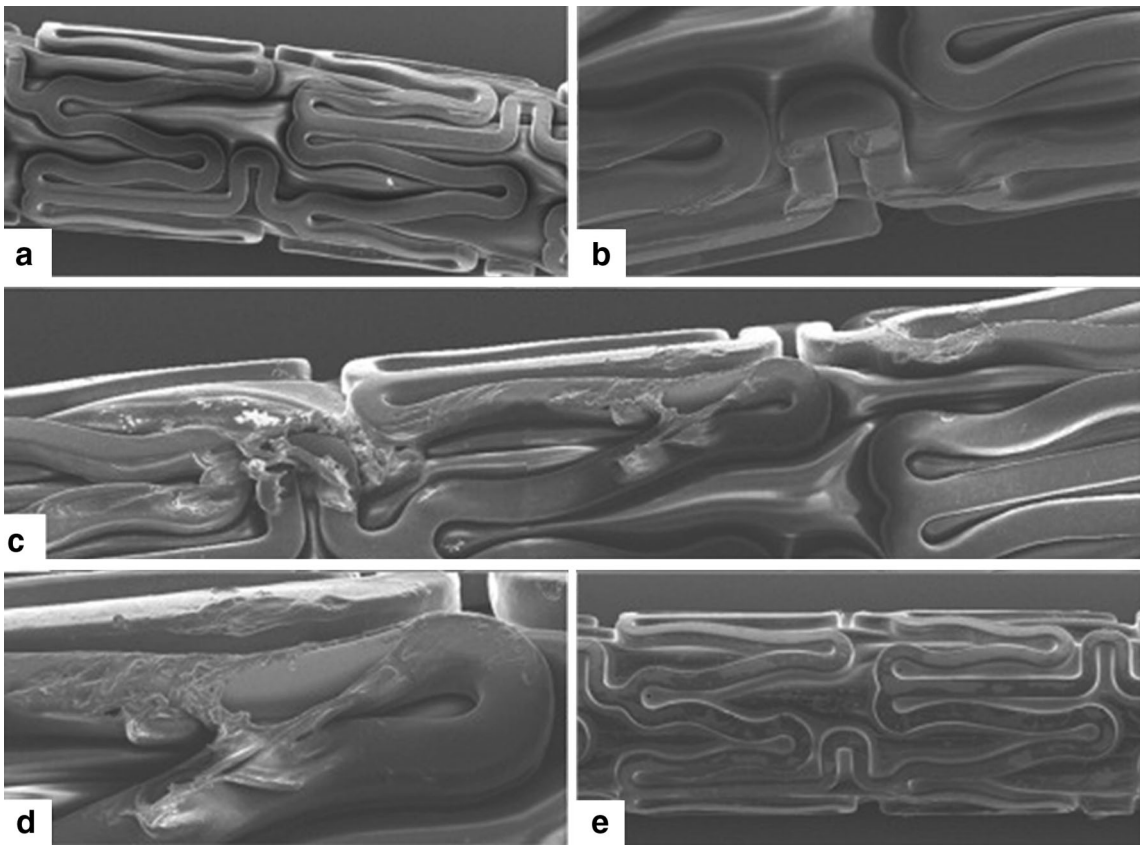

Fig. 4 Scanning electron microscopy showing damage and no damage to polymer. Scanning electron microscopy showed damage to polymer of the everolimus-eluting stent that would not advance to the lesion (**a**–**d**). By contrast, there was no damage to the polymer of the everolimus stent that was delivered without significant resistance after rotational atherectomy (**e**). Reprinted from Kuriyama et al. [38]

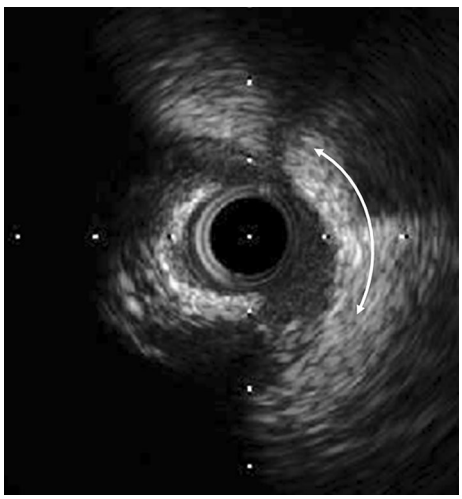

Fig. 5 Eccentrically calcified plaque. Intravascular ultrasound shows eccentrically calcified plaque along with a normal segment (*double-headed white arrow*). Coronary artery perforation may occur due to overstretching the normal segment using an oversized balloon/stent

Optimal DES sizing and edge landing zone

There exist no optimal IVUS criteria for stent sizing. Clinically, true vessel or mid-wall stent/balloon sizing is frequently used on the basis of distal reference vessel diameter [1, 71].

Previous studies have suggested that stent edge plaque burden is a predictor of stent edge restenosis and that inadequate lesion coverage is associated with stent edge restenosis [55–57, 72]. Therefore, stent edge restenosis can be minimized by stenting from normal to normal segment. However, since reference segments are rarely normal, stent edge landing zone should be within a segment with a plaque burden of less than 50% [56, 58–60]. Moreover, Fujii et al. reported that independent predictors of early stent thrombosis were a significant residual reference segment stenosis [52]. Costa et al. extended the concept of geographic miss to DES and showed that injured or diseased segments not covered by DES was associated with

increased risk of 1-year target vessel revascularization and myocardial infarction [72]. IVUS guidance can provide assessment of optimal DES landing zone and ensure optimal lesion coverage to minimize DES edge restenosis and DES early thrombosis.

Stent underexpansion

Several studies have demonstrated that minimum stent area (MSA) is a predictor of in-stent restenosis and stent thrombosis [52, 61]. The SIRIUS (SIRolImUS-Eluting Balloon Expandable Stent in the Treatment of Patients With De Novo Native Coronary Artery Lesions) substudy showed that sirolimus-eluting stents had a lower optimal MSA cutoff (5.0 mm^2) compared to bare metal stents (6.5 mm^2) to predict adequate follow-up patency [61]. The TAXUS substudy reported that optimal MSA cutoff for the prediction of in-stent restenosis were 5.7 mm^2 for paclitaxel-eluting stents [62]. Another study reported that the optimal MSA cutoffs to predict restenosis were similar among sirolimus-, zotarolimus-, and everolimus-eluting stents; 5.5, 5.3, and 5.4 mm^2, respectively, and that MSA >7 mm^2 for the second generation DES indicated a very low probabilities of angiographic restenosis [54]. Underexpansion after sirolimus-eluting stent implantation for in-stent restenosis was also shown to be a risk factor of re-restenosis [63]. In LMCA bifurcation lesions, Kang et al. showed that MSA cutoffs for sirolimus-eluting stents to predict in-stent restenosis were 5.0 mm^2 (ostial LCX), 6.3 mm^2 (ostial LAD), 7.2 mm^2 (polygon of confluence of the LAD and LCX), and 8.2 mm^2 (LMCA above the polygon of confluence) [64].

Stent malapposition

IVUS studies have reported that late stent malapposition is a predictor of late/very late stent thrombosis and more frequently identified in patients with DES compared with bare metal stents [69]. Another study showed that the greater the acute stent malapposition, the higher the possibility of its persistence at follow-up [70]. Several factors have been reported to be responsible for late stent malapposition as follows: (1) acute stent malapposition due to stent underexpansion or smaller stent diameter than reference lumen diameter; (2) chronic stent recoil; (3) thrombus dissolution; (4) positive vessel remodeling, and (5) inadequate neointimal hyperplasia [73]. IVUS guidance can allow us to identify acute stent malapposition that is treatable when detected by IVUS, and to reduce the likelihood of late stent malapposition and subsequent late/very late stent thrombosis.

Stent edge dissection and intramural hematoma

The incidences of stent edge dissection range from 5 to 23% of the PCI procedures as detected by IVUS [74]. Maehara et al. reported that 60% of intramural hematomas were angiographically detected as a dissection and 11% as a new stenosis, and that no significant angiographic abnormality was detected in 29% of patients with intramural hematoma [75]. Recent IVUS studies showed that greater stent expansion, stent edge asymmetry, residual plaque eccentricity, and large, calcified, and/or attenuated plaques at stent edges were predictors of stent edge dissection [76, 77], and that stent edge dissection, especially with a small lumen area, was a predictor of early stent thrombosis and restenosis [66, 77, 78]. The HORIZONS-AMI (A Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) substudy showed that stent edge dissection with lumen narrowing <4 mm^2 or dissection angle $>60°$ was associated with early stent thrombosis after PCI for acute myocardial infarction [66].

Tissue (plaque or thrombus) protrusion

Tissue protrusion is frequently detected by IVUS, especially in unstable lesions. The ADAPT-DES IVUS substudy [79] reported that the overall prevalence of tissue protrusion detected by IVUS was 38.5% per patients and 34.3% per lesion; 54.3% in patients with ST-segment elevation myocardial infarction, 46.1% in non-ST-segment elevation myocardial infarction, 34.3% in unstable angina, and 30.6% in stable ischemic heart disease. The positive predictors of tissue protrusion were age, body mass index, ST-segment elevation or non-ST-segment elevation myocardial infarction, right coronary artery, Thrombolysis In Myocardial Infarction flow grade 0/1, total stent length, maximal device diameter, and stent expansion, whereas the negative predictors were statin treatment before admission and calcified lesions. Tissue protrusion was also associated with periprocedural enzyme elevation. At 2-year follow-up, there was no significant difference in incidence of cardiac death, myocardial infarction, or stent thrombosis between patients with and without tissue protrusion.

Chronic kidney disease

Patients with chronic kidney disease comprise a challenging subset with increased morbidity and mortality [80, 81] including the need for renal replacement therapy. Established approaches to prevent contrast-induced nephropathy include periprocedural hydration [82] and minimizing contrast volume [80]. A randomized trial demonstrated that IVUS-guided PCI markedly reduced the volume of contrast

agent compared with angiography guidance [83]. Moreover, Ali et al. reported a strategy for sequential diagnostic angiography using ultra-low volume of contrast followed by IVUS- and physiology-guided zero contrast PCI in patients with advanced chronic kidney disease [84].

Conclusions

Available evidence on the clinical utility of IVUS-guided DES implantation has been increasing. IVUS-guided PCI allows us to optimize DES implantation and to minimize adverse cardiac events.

Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Conflict of interest The authors declare that they have no conflict of interest.

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